REMARKS

The Examiner is thanked for the very detailed and thorough Office Action. Pursuant to that Office Action, claims 1, 5, 7, 10 and 12 have been rewritten to more definitely set forth the invention and obviate the rejections. In particular, claim 1 has been amended to incorporate the subject matter of original claim 5. Also, claim 5 has been rewritten as an independent claim to incorporate the subject matter of original claims 1, 3-5, 7-9, and 12-14. Claim 10 has been rewritten in independent format, to include the limitations of claim 1 and previous claim 5. Claim 12 has been rewritten to be dependent upon claim 3 rather than claim 2 which has been cancelled. The present amendment is deemed not to introduce new matter. The present amendment is believed to raise no new issues requiring new searching or consideration since the current amendment merely combines a number of claims which have been previously considered by the examiner. Claims 1 and 3-20 remain in the application.

Reconsideration is respectfully requested of the rejection of Claims 1 and 12 under 35 U.S.C. 102(b) as being unpatentable over Crawford, et al.

The Present Invention

The specification herein indicates on page 3, lines 9-27, that 'although the combined use of electroporation and iontophoresis has also been studied, there have been no reports that a sufficient amount of insulin was delivered by such a combined use to such an extent that the effects of the insulin delivered were observed. Regarding an attempt to cause drugs other than insulin to be percutaneously absorbed by the combined use of eletroporation and iontophoresis, there has been a report that calcitonin with a molecular weight of 3000 could be delivered to such an extent that a rat had a blood calcitonin level of a few hundred ng/mL, but that PTH with a molecular weight

of 4000 could be delivered only in small amounts that were less than 100 ng/mL" (Journal of Controlled Release, Vol. 66, p.127, 2000). This is to say, under the current circumstances, it is difficult to deliver compounds with a molecular weight of more than 3000 by the combined use of electroporation and iontophoresis. Furthermore, it is also difficult to deliver a sufficient amount of insulin, which has a molecular weight of 6000, through the skin or mucosa. A copy of the "Journal of Controlled Release, Vol. 66, pages 127-133, 2000, is attached hereto.

In view of the experimental data described in the above article in the "Journal of Controlled Release", it is strongly urged that one skilled in the art would not consider it obvious to administer insulin lispro having a molecular weight of about 6000 by the combined means of electroporation and iontophoresis.

Moreover, Crawford, et al. nowhere discloses administration of "insulin lispro" by the combined means of electroporation and iotophoresis.

Notwithstanding strong evidence of non-obviousness such as in the above-referenced "Journal of Controlled Release", the present inventors attempted to administer various types of insulin, human insulin, swine insulin, bovine insulin, arginine-insulin, and insulin lispro in comparative tests. As a result, the present inventors unexpectedly and surprisingly found that when insulin lispro represented by the structural formula indicated in claim 1 or a pharmaceutically acceptable salt thereof is used and electroporation is combined with iontophoresis as a means for applying electric fields, excellent percutaneous or submucous absorptivity of the drug can be achieved. It was also found that the drug can exhibit sufficient beneficial effects and maintain such effects for a long period (see Specification, page 4, lines 11-24).

The comparative tests are shown as the examples in this application on page 18, line 13, to page 27, line 24, and Figs. 7-12.

In summary, it is respectfully urged that the prior art articles such as in the above-referenced "Journal of Controlled Release" as well as the comparative tests in the present application present overwhelming evidence of non-obviousness with respect to the invention claimed herein.

The Crawford, et al. Patent

Crawford, et al. disclose delivering drugs, pharmaceuticals, plasmids, genes and other agents into living bodies using the combination of iontophoresis and electroporation. In this connection Crawford,et al. disclose numerous human maladies for which drugs are delivered, including open heart surgery and chemotherapy (column 3, lines 24-48, and column 5, lines 1-7).

However, there is no disclosure whatever in Crawford, et al. of combining iontophoresis and electroporation in the treatment of diabetes, nor is there any disclosure of administering either human insulin or synthetic analogs of human insulin for the treatment of diabetes. In view of the known difficulty of administering a high molecular weight compound with a molecular weight of almost 6,000 using either electroporation or iontophoresis, it is respectfully submitted that one of ordinary skill in the art with only the Crawford, et al. reference before them would not consider combining iontophoresis with electroporation for the treatment of diabetes with insulin lispro. On the contrary, it is respectfully urged that one of ordinary skill in the art would not use electroporation or iontophoresis for treating diabetes because of the known difficulty in delivering an effective amount of insulin lispro by this method of administration.

As indicated above, claim 1 has been rewritten to incorporate the subject matter of original claim 5, that is, that the insulin lispro is dissolved, suspended, or dispersed in a hydrophilic matrix. It is respectfully submitted that there is no disclosure or suggestion in Crawford, et al. of this newly added feature to claim 1. For this reason, it is believed that claim 1 as amended is neither anticipated by nor unpatentably obvious over Crawford, et al. Consequently, the examiner would be justified in no longer maintaining the rejection. Withdrawal of the rejection is accordingly respectfully requested.

Reconsideration is respectfully requested of the rejection of claims 3, 4, 15-17, and 20 under 35 U.S.C. 103(a) as being unpatentable over Crawford, et al. in view of Mori, et al.

The deficiencies of the Crawford, et al. patent are discussed above.

To cure the deficiencies of the primary reference of Crawford, et al., the examiner now relies upon the secondary reference of Mori, et al. for the proposition that Mori, et al. disclose the overall design of the electrodes including the presence of a membrane and operating ranges. Although Mori, et al. disclose administering insulin and calcitone using the device disclosed therein (page 3, paragraph [0035]), there is no disclosure in Mori, et al. of an apparatus and method of administering an effective amount of a high molecular weight compound such as insulin lispro. It is respectfully urged that neither the primary reference of Crawford, et al. nor the secondary reference of Mori, et al. disclose administering an effective amount of insulin lispro using the combination of electroporation and iontophoresis. On the contrary, that teaching or suggestion comes only from the present application and constitutes an important element or aspect of the present invention.

It is respectfully urged that the examiner's combination of references neither anticipate nor render unpatentably obvious the subject matter now called for in the claims herein. This is especially buttressed by the fact that it was known in the art as evidence by the attached "Journal of Controlled Release" article discussed above, that effective amounts of compounds having a molecular weight greater than 3000 cannot be administered using electroporation, iontophoresis, or a combination thereof.

For these reasons, it is respectfully urged that the examiner would be justified in no longer maintaining the rejection. Withdrawal of the rejection is accordingly respectfully requested.

Reconsideration is respectfully requested of the rejection of claims 5-6 as being unpatentable under 35 U.S.C. 103(a) over Crawford, et al. in view of Jacobsen, et al.

The deficiencies of Crawford, et al. are discussed above.

In an effort to cure the deficiencies of Crawford, et al., the examiner relies upon Jacobsen, et al. for the disclosure of using a hydrophilic matrix in iontophoresis. Jacobsen, et al. is concerned principally with the use of a bioelectrode for use in the iontophoretic delivery of ions into the skin or tissue of a person. However, there is no disclosure whatever in Jacobsen, et al. of using a combination of electroporation and iontophoresis to deliver an effective amount of insulin lispro. On the contrary, that teaching or suggestion comes only from the present application and constitutes an important element or aspect of the present invention.

In view of these deficiencies, it is respectfully urged that the examiner would be justified in no longer maintaining the rejection. This is especially true since claim 5 has been rewritten to include the subject matter of claims 1, 3-5, 7-9, and 12-14. It is respectfully submitted that none

of the examiner's references of record disclose the device called for in amended claim 5 herein. Withdrawal of the rejection is accordingly respectfully requested.

Reconsideration is respectfully requested of the rejection of claims 7-10 and 18 under 35 U.S.C. 103(a) as being unpatentable over Crawford, et al. in view of Mori, et al.

The deficiencies of Crawford, et al. and Mori, et al. are discussed above.

It is respectfully urged that the examiner's combination of references taken either individually or in combination failed to disclose the essential aspect of the present invention. That is, these references failed to disclose or suggest using the combination of electroporation and iontophoresis to administer an effective amount of insulin lispro. Consequently, the examiner would be justified in no longer maintaining the rejection. Withdrawal of the rejection is accordingly respectfully requested.

Reconsideration is respectfully requested of the rejection of claims 11 and 19 under 35 U.S.C. 103(a) as being unpatentable over Crawford, et al. in view of Mori, et al. and further in view of Murdock.

The deficiencies of Crawford, et al. and Mori, et al. are discussed above.

Although Murdock discloses an electrode assembly and method of forming an anhydrous reservoir layer of an electrode assembly in an electrotransport transdermal agent delivery device, there is no disclosure or suggestion in Murdock of using electroporation and iontophoresis to deliver an effective amount of insulin lispro. For this reason, the examiner's combination of references fails to disclose the invention called for in the claims herein. Withdrawal of the rejection is accordingly respectfully requested.

Reconsideration is respectfully requested of the rejection of claims 13 and 14 under 35

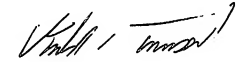
U.S.C. 103(a) as being unpatentable over Crawford, et al. in view of Miller, et al.

The deficiencies of Crawford, et al. are discussed above.

In order to cure the deficiencies of Crawford, et al., the examiner relies on Miller, et al. for the disclosure of using multiple electrodes and a power supply for iontophoresis. Although Miller, et al. is concerned primarily with a method of increasing the battery life of an alternating current iontophoretic device used to transport a compound through a localized region of a patient's body, there is no disclosure in Miller, et al. of using the combination of electroporation and iontophoresis to deliver an effective amount of insulin lispro. It is therefore respectfully urged that Miller, et al. fails to cure the deficiencies of Crawford, et al. and, therefore, it is respectfully urged that the examiner's combination of references do not render the claims unpatentably obvious. Withdrawal of the rejection is accordingly respectfully requested.

In view of the foregoing, it is respectfully submitted that the application is now in condition for allowance, and early action and allowance thereof is accordingly respectfully requested. In the event there is any reason why the application cannot be allowed at the present time, it is respectfully requested that the Examiner contact the undersigned at the number listed below to resolve any problems.

Respectfully submitted,



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